Author's response to reviews

Title: Laboratory Testing for Cytomegalovirus among Pregnant Women in the United States: a Retrospective Study using Administrative Claims Data

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Dr. Philippa Harris  
Executive Editor  
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Dear Dr. Harris,

We would like to thank you for reviewing this article (Manuscript #: 2876809917521427, Laboratory Testing for Cytomegalovirus among Pregnant Women in the United States: a Retrospective Study using Administrative Claims Data), and considering the article for inclusion in *BMC Infectious Diseases*. We would like to thank Drs. Hamprecht and Grangeot-Keros for their thoughtful review of this manuscript. Below are our responses to their comments.

**Reviewer 1: Klaus Hamprecht**

1. **Commercial database.**  
   Is the database using MarketScan® really representative for the American society respectively health assurance system or does it produce a bias? To my knowledge in the US health assurance is not obligatory and ethnical minorities are not included adequately. We know that the highest rates of cCMV were reported from black cohorts in Birmingham/Alabama (Stagno/Pass/Fowler) Is there a bias by the kind of software which may be different using another software from an other company?

   *Author response: We agree that the MarketScan Commercial databases are not reflective of the entire US population since they primarily include those with employer-sponsored insurance. Age and sex distributions in those databases are comparable to the US population with employer-sponsored insurance, but there is no information on race in MarketScan Commercial databases. Other research has shown that populations with employer-sponsored insurance tend to include a higher proportion of high-income and white populations relative to people with either public insurance or no health insurance. For example, one published analysis of the MarketScan Commercial and Medicaid databases found that the frequency of sickle cell disease (SCD) among children was 1 in 850 in the Medicaid sample and 1 in 4,800 in the Commercial sample. The overall prevalence of SCD among children in the US is probably between 1 in 2,000 and 1 in 2,500. An all-payers claims database could accurately represent the population of a given state, and several states are in the process of setting up such databases. There is no evidence to believe that the MarketScan Commercial databases are less representative of*
the US population with private insurance than is true of other commercial healthcare databases.

We have included in the discussion: “The MarketScan population is not representative of the national population since the data represents a large convenient sample primarily of individuals with private employer insurance, which accounts for 56% of the US population in 2009 [29]. People with employer-sponsored insurance are less likely to be low-income or non-white than are uninsured or publicly-insured people [30]. Separate MarketScan databases exist with healthcare claims data for the Medicaid population and it would be useful to examine CMV testing rates in the population with publicly-financed health insurance.” [Page 10, lines 17-23]

Why the authors computed frequencies of pregnant women with a code for “CMV disease” and CMV testing. Diagnosis of CMV primary infection is just by accident, because in 75% of all cases the CMV primary or recurrent infection during pregnancy is without any symptom or with very unspecific symptoms.
Author response: We agree that most CMV primary infections during pregnancy are asymptomatic and are likely undiagnosed without any testing. However, we were still interested in evaluating rates of CMV-specific testing among those with a diagnostic code for CMV disease to see if these diagnoses are primarily made by clinical assessment alone, or in combination with laboratory testing.

We have added this to the methods: “We computed frequencies of pregnant women with a code for CMV disease and CMV-specific testing to evaluate whether a pregnant woman had a diagnostic code for CMV disease based on clinical assessment alone, or also in combination with laboratory testing.” [Page 6, lines 4-6]

3. The quality of the disease parameter “CMV mononucleosis”.
In Table 1 is shown, that >96% of all pregnant women are older than 20 years and 56% older than 30 years. Reflecting that “Mononucleosis” is an infection of the adolescence in most part of people below 20 years, only 4% of data of the study would fit with it (Table 1, Age group 15-19).
Author response: We agree that a diagnostic code of mononucleosis is not a highly sensitive indicator of CMV infection during pregnancy since a very small proportion of pregnant women with CMV infection will manifest with mononucleosis-like syndrome (Stagno S, Infectious Disease of the Fetus and Newborn Infant 2006). However, we included this in our analysis because it is a potential indicator of maternal infection and may potentially be used to prompt providers to consider CMV infection in pregnant women with mononucleosis syndrome, which we included in the discussion: “Although CMV infection is often asymptomatic, CMV infection should be considered as part of the differential diagnosis in pregnant women who present with mononucleosis-like symptoms”.
[Page 8, lines 10-12] Infectious mononucleosis is most commonly caused by primary EBV infection and in these cases, usually affects those who have primary EBV infection during or after the second decade of life (Luzuriaga K, N Engl J Med 2010). However, differential diagnosis of mononucleosis syndromes (which are characterized by pharyngitis,
lymphadenopathy, and malaise) includes CMV infection (Luzuriaga K, N Engl J Med 2010) which can occur among adults (Rodríguez-Baño J, Clin Microbiol Infect. 2004).

We have added the following text to the methods to provide more information related to infectious mononucleosis as a potential symptom of primary CMV infection in pregnant women: “Since mononucleosis is a potential symptom and possible indication of maternal CMV infection[8], we examined rates of pregnant women with a diagnostic code for mononucleosis. Although infectious mononucleosis is a clinical syndrome commonly associated with primary Epstein-Barr virus infection during or after second decade of life[22], adults with primary CMV infection may also develop mononucleosis-like syndromes[23]” [Page 5, lines 19-23].

4. Type of CMV testing
The authors refer to Dollard et al, 2011 for diagnosis of CMV primary infection in pregnancy in context of the absence of CMV IgG avidity testing in the USA. (page 3). The adequate diagnosis of CMV primary infection in pregnancy is based on serology (Lazzarotto et al, 2011; Revello et al, 2004). But without IgG avidity its impossible to differentiate between CMV primary infection or recurrent infection. Thus all different test shown in Table 2 lack the most important tool for diagnosis of recent infection: the low avidity detection. IgM titers may persist over months, IgM titers may differ strongly using tests from different companies. The only option using only CMV IgG/IgM data would be to check reducing IgM indices, which has need for sequential examinations. And these are mostly not done. PCR does not help for routine diagnosis, because CMV shedding into urine is detectable during every period of CMV primary infection and viral DNAemia has a small window of about 2 weeks around primary infection (Lazzarotto et al., 2011): Virus culture, DFA, as shown in Table 2 do they have a real diagnostic value?

Author response: We agree that primary CMV infections during pregnancy through serology can only be done by showing sero-conversion or a combination of IgG avidity testing, IgM, and IgG testing. We have added the following sentence in the introduction to clarify this: “Diagnosis of CMV infection among otherwise healthy adults generally relies on serologic testing; proposed algorithms have included documentation of seroconversion or detection of specific IgM antibody in association with low IgG avidity” [Page 3, line 16-19].

Unfortunately, there is no CPT code for CMV IgG avidity testing and therefore we were unable to determine rates of IgG avidity testing. This has been added in the discussion: “There is no CPT code for CMV IgG avidity testing and therefore we were unable to determine rates of IgG avidity testing. “ [Page 10, lines 5-7]. Lab results were also unavailable, as mentioned in the methods: “Evidence of laboratory confirmation of CMV infection was not included in the CMV case definition because laboratory testing results were not available in the MarketScan database. [Page 5, line 23-Page 6, line 1]

Due to limitations in this database, we would be unable to identify whether laboratory testing was able to identify primary CMV infections in pregnant women; we can only look at frequency of claims for CMV-specific testing, types of tests, and estimate when the tests were performed during pregnancy. Although serological assays are the optimal means of diagnosing primary CMV infection during pregnancy, we were still interested in identifying
the types of CMV-specific tests performed since there is no published information on this in the United States.

5. The role of table 4 remains quite unclear.
   Author response: As mentioned in the discussion, not all prenatal laboratory tests are captured in claims databases for a number of reasons, such as global billing (where providers submit a bundled claim for comprehensive prenatal care services instead of each service separately). The role of table 4 was to provide information on how sensitive the database was in detecting prenatal laboratory tests by looking at rates of routinely performed prenatal laboratory tests. This is explained in the methods on page 6, lines 11-14: "To better understand the possible sensitivity of the 2009 MarketScan Commercial databases for detecting claims for CMV-specific laboratory testing, we calculated frequencies of pregnant women with ≥1 codes for other laboratory tests that are recommended by the American College of Obstetricians and Gynecologists to be routinely performed during pregnancy". We have also added this information in the results: “To assess the sensitivity of the MarketScan database in capturing CMV-specific testing during pregnancy, we calculated frequencies of other routinely recommended prenatal that are conducted for all pregnant women as part of standard prenatal care [Table 4].” [Page 7, lines 9-11]

Table 4 also provides information on rates of CMV-specific testing in this group of pregnant women with claims for other routinely performed prenatal tests since we expected that their claims would be more complete. However, rates of CMV-specific testing among these women with potentially more completely claims data were still low (1.5-4.2%), as we mentioned in the discussion: “It seems unlikely however that CMV testing rates among pregnant women are much higher than those we report as we did not find substantially higher testing rates even among pregnant women for whom claims for other routine laboratory tests recommended during pregnancy were captured in the MarketScan Commercial database.” [Page 10, lines 10-14]

Reviewer 2: Liliane Grangeot-Keros

1. The authors must explain how they calculated the very low rate of fetal transmission after non-primary infection (0.2-2%), as it is almost impossible to diagnose non-primary infection.
   Author response: We agree that it is difficult or unusual to diagnose non-primary infection because the needed tests may not be done or because there is not clear consensus as to what constitutes evidence or lack of evidence of a non-primary infection. The rates we used were based on a review by Kenneson et al (Rev Med Virol 2007). They looked at published epidemiologic studies related to congenital CMV infection and examined birth/fetal prevalence of recurrent infections. Recurrent infection was defined as being IgG positive prior to pregnancy, IgG positive at the first pregnancy visit without IgM test, or IgM positive with high IgG avidity.

   We have clarified this in the introduction section of the manuscript by editing the text to read: “The risk of CMV transmission to the fetus is higher among pregnant women with primary infection compared to those who were IgG positive prior to pregnancy. IgG
positive at their first pregnancy visit, or IgM positive with high IgG avidity and therefore presumed to have non-primary infection (30-40% compared to 0.2-2%).” [Page 3, lines 6-9]

2. Page 3, line 14: typing error ("demonstrating" and not "demostrating")
   Author response: We have fixed this typo. [Page 3, line 20]

3. Page 7: the rate of testing for CMV (16%) in patients with a diagnosis of mononucleosis is not the same as the rate given in the results (14%) on page 6.
   Author response: We have fixed this typo, so the sentence now reads: “We found higher rates of testing among patients in our study population with a diagnosis of mononucleosis, a symptom potentially attributable to CMV infection, but the rate of testing for CMV was only 14% even in this high-risk group.” [Page 8, lines 8-10]

4. Page 9: Regarding the prevention study conducted in France, the authors say that the French study presents limitations because it does not have a control comparison group, but the use of this kind of group would have not been ethic during pregnancy!
   Author response: We have added that the study did not have a comparison group as the study investigators deemed this unethical: “However, adherence to recommended preventative measures was not monitored and the study did not use a randomized design because the investigators deemed it unethical.” [Page 9, lines 16-18]

Please do not hesitate to contact me if you need any further questions. Thank you again for considering our manuscript for publication in BMC Infectious Diseases.

Sincerely Yours,

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